

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



GDA

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61L 27/00	A2	(11) International Publication Number: WO 00/32247 (43) International Publication Date: 8 June 2000 (08.06.00)
(21) International Application Number: PCT/US99/27190		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 16 November 1999 (16.11.99)		
(30) Priority Data: 09/197,809 23 November 1998 (23.11.98) US		
(71) Applicant: HEALTHSHIELD TECHNOLOGIES LLC [US/US]; Suite 201, 67 Prospect Avenue, West Hartford, CT 06106 (US).		
(72) Inventors: TROGOLO, Jeffrey, A.; 228 Commonwealth Avenue, Boston, MA 02116 (US). BARRY, John, E.; 18 Drake Lane, Derry, NH 03038 (US). HOLLEY, Steven; 24 Bigelow Street, Brighton, MA 02135 (US).		
(74) Agents: GOGORIS, Adda, C. et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022-7513 (US).		

(54) Title: ANTIMICROBIAL FABRIC AND MEDICAL GRAFT OF THE FABRIC

(57) Abstract

A medical graft, such as a vascular graft, made of a fabric containing an inorganic antimicrobial agent. The fabric has a coating material with the inorganic antimicrobial agent bonded to it, the agent preferably being a zeolite. The fabric can be porous so as to permit tissue to grow on it with the fabric pores providing attachment sites for the tissue. Alternatively, the fabric can be coated with a tissue biocompatible material, such as collagen. A porous fabric applicable for the graft, and for other medical uses, and a method of manufacturing the porous fabric having a coating thereon to which is bonded an antimicrobial agent, such as a zeolite, also is provided. The fabric is antimicrobial, remains pliable, and is also porous.

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Antimicrobial Fabric and Medical Graft of the Fabric

Field of the Invention

The present invention relates to a fabric having antimicrobial properties and a
5 medical graft, such as a vascular graft, made of such fabric.

Background of the Invention

Various types of grafts are used in the human body for surgical replacement
and repair. A graft is a tubular type member typically used to provide a passage for fluid
10 flow between two parts of a vein or artery that has been severed or as a bypass for diseased
or deteriorated tissue. For example, grafts are often used in vascular bypass applications,
such as for an abdominal aortic aneurism. The graft can either be of natural material, taken
from another part of the body of a human or an animal, or it can be of synthetic material.
Where the graft is of synthetic material, it would be desirable for it to be able to inhibit the
15 growth of bacteria in the fluid flowing in the graft or from other body parts that come into
contact with the graft. Other medical products, such as pledges and patches, would also
desirably have the same properties.

Brief Description of the Invention

20 The present invention is directed to a graft for medical use that is made of a
fabric constraining an inorganic antimicrobial agent. The fabric has the inorganic
antimicrobial agent bonded to it, the agent preferably being a zeolite. In the vascular graft
application, the fabric fibers are preferably of Teflon or polyester. The fabric can be porous
so as to permit tissue to grow on it with the fabric pores providing attachment sites for the
25 tissue. Alternatively, a non-porous fabric is coated with a tissue biocompatible material,
such as collagen, which also can be coated on a porous fabric.

The present invention also is directed to an antimicrobial fabric applicable for
the graft, and for other medical uses, having a coating thereon to which is bonded an
antimicrobial agent, such as a zeolite. When the fabric is porous, it remains pliable and

flexible. This type of fabric, which is pliable, has use for other types of medical products such as pledges and patches.

In a preferred method of manufacturing the porous fabric, the fabric is held under tension in one direction and a mixture of an adherent type coating material, such as a hydrophilic polymer or silicone, is applied which covers the fabric fibers and fills the spaces between the fibers. With the fabric held in tension in both directions, a dusting of the antimicrobial agent is applied onto the coating material while it is still wet. This bonds the agent to the coating material. The fabric is then cured with a pressurized gas, such as air, to dry it. The air under pressure removes all of the matter, coating material and antimicrobial agent, from between the fibers making it porous allowing it to be pliable. In another embodiment, the antimicrobial agent is mixed with the coating material, the mixture is applied to the fabric and the matter between the pores is removed by the pressurized air drying.

If the step of pressurized air drying is omitted, the fabric will dry with the coating material and antimicrobial agent present in the pores as well as with the antimicrobial agent bonded to the fabric fibers. Here, since the fabric does not have pores for tissue attachment sites it is preferred that the fabric be coated with a tissue growth promoting material, such as collagen.

The antimicrobial agent is on the surface of the fabric bonded to the coating material and is available to provide antimicrobial action relative to fluids and body parts that come into contact with it.

Objects of the Invention

An object of the invention is to provide a medical graft of a fabric containing an inorganic antimicrobial agent.

Another object is to provide a medical graft of a fabric containing an inorganic antimicrobial agent that is coated with a tissue compatible material.

A further object is to provide a porous and pliable antimicrobial fabric useful for medical applications and a method of manufacturing the same.

Still another object is to provide a porous, pliable antimicrobial fabric useful for a medical graft.

Yet a further object is to provide a vascular graft utilizing a porous fabric having antimicrobial properties.

Brief Description of the Drawings

Other objects and advantages of the present invention will become more apparent upon reference to the following specification and annexed drawings in which:

5 Fig. 1 is a perspective view of a base fabric;
 Fig. 2 is a cross-sectional view along lines 2-2 of Fig. 1
 showing application of the coating material to the fabric;
 Fig. 3 is a cross-sectional view of the fabric after the antimicrobial agent has
 been applied;
 Fig. 4 is a cross-sectional view of the finished fabric after drying;
10 Fig. 5 is a view of a vascular graft using the fabric of the invention.

Detailed Description of the Invention

All patents, patent applications, and publications listed herein are hereby incorporated by reference in their entireties.

15 Fig. 5 illustrates a vascular graft 70 made with the inorganic antimicrobial fabric. While the graft illustrated is of the pleated type, such as shown in U.S. patent 5,607,464, it can be of the more conventional type that has no pleats. The graft 70 is of the generally overall cylindrical construction so that it can be attached between the ends of the body tissue to be connected or used as a bypass. The antimicrobial fabric 72 forming the
20 graft is of one of the types described below.

The outer surface of the graft of Fig. 5 is shown as being coated with a tissue compatible material 74 which can promote tissue growth, such as collagen. The collagen coating is usually used where the fabric is completely coated with the antimicrobial agent. If the graft fabric is porous, it normally is left uncoated since the presence of pores in the fabric
25 provides sites for tissue attachment. However, a porous fabric also can be coated with collagen.

Various types of antimicrobial fabrics useful for the graft 70 are described.

1. Coated fabric that is porous Figs. 1-4 describe a porous antimicrobial fabric and method of manufacture useful for the graft and which also has other medical uses due to its pliability. In Fig. 1, there a base material comprising a piece of fabric 10 of the mesh type formed by fibers 12 which are laid transverse to each other and which define spaces, or pores, 14 between the fibers. The fibers can be of any suitable material, for example, cotton, nylon polyester, Teflon, e-PTFE and blends of these materials. For the

graft application, Teflon or polyester is preferred. The fabric can be either of the woven or non-woven type. The fabric 10 is shown by the arrows T as being able to be held under tension in both directions generally along the fabric length and width, in the directions of the cross-laid fibers, by any suitable mechanism (not shown), for example, rollers, clamps, etc..

5 Fig. 2 shows the fabric piece 10 in the stage of having an coating of an adherent material 18 applied to one surface. It should be understood that the invention is applicable to performing the process on both fabric surfaces and on the sides of the fabric fibers forming the pores 14. The adherent coating material 18 is a biologically compatible material such as, for example, acrylic, polyurethane, silicone, latex, polyglycolic lactic acid
10 or other biodegradable polymer, especially one that is a hydrophilic, a non-degrading polymer such as a hydrophilic polyurethane, for example TECOPHILIC which is made by Thermedics. These materials all have elastomeric properties.

In a preferred embodiment of the invention, the fabric coating material 18 is applied as a mixture of a high strength RTV dispersed in a solvent, such as xylene. A
15 preferred composition of the mixture is 50% RTV and 50% xylene although the ratio of the two materials can be varied. Increasing the proportion of the coating material in the mixture makes the final fabric product less pliable.

In a preferred manner of application of the coating material, the fabric 10 is held under tension in its lengthwise dimension. The coating material mixture 18 is supplied
20 by a peristaltic pump to an ultrasonic disperser. The ultrasonic disperser creates a fine mist of the mixture that is blown out of the disperser by an air source, illustratively shown by reference numeral 19, to coat the fabric 10. There can be one or more dispersers and air sources on both sides of the fabric and at varying angles to fully coat the entire surfaces of the fabric fibers. Alternatively, only one surface is coated, the two surfaces are coated
25 sequentially, or both surfaces coated at the same time. In the application for the vascular graft, the fabric preferably is coated on both surfaces.

Fig. 3 shows the fabric 10 having been coated on one side with the coating material 18. As seen, the coating material 18 extends into the openings 14 between the fibers of the fabric and also coats the top of each of the fibers. There is a continuous layer of the
30 coating material 18 over the entire surface of the fabric at this stage of the process. The fabric can be cycled relative to the disperser as many times as needed. That is, the deposition of the coating material mixture on the fabric can be accomplished by applying a desired number of layers to achieve a desired thickness. The layers are contiguous to and mixed

with each other. The depth of the coating material 18 on top of the fabric is selected to be between 0.01 and 50 microns, more preferably between 0.1 and 25 microns, and most preferably between 0.1 and 10 microns.

As is also shown in Fig. 3, an inorganic antimicrobial agent 20 in powdered form is applied to the coating material 18 while it is still wet. During this step the fabric preferably is held under tension in both directions, that is, generally along both the fabric length and width. The powdered antimicrobial agent 20 becomes immersed into and bonds with the coating material layer 18 on the fabric.

As to the inorganic antimicrobial agent 20, a number of metal ions, which are inorganic materials, have been shown to possess antibiotic activity, including silver, copper, zinc, mercury, tin, lead, bismuth, cadmium, chromium and thallium ions. These antibiotic metal ions are believed to exert their effects by disrupting respiration and electron transport systems upon absorption into bacterial or fungal cells. Antimicrobial metal ions of silver, gold, copper and zinc, in particular, are considered safe even for *in vivo* use. Antimicrobial silver ions are particularly useful for *in vivo* use due to the fact that they are not substantially absorbed into the body. That is, if such materials are used for the antimicrobial fabric, they should pose no hazard to the body.

Antibiotic zeolites also are suitable as the agent. These have been prepared by replacing all or part of the ion-exchangeable ions in zeolite with ammonium ions and antibiotic metal ions, as described in U.S. Patent Nos. 4,938,958 and 4,911,898. Such zeolites have been incorporated in antibiotic resins (as shown in U.S. Patent Nos. 4,938,955 and 4,906,464) and polymer articles (U.S. Patent No. 4,775,585). Polymers including the antibiotic zeolites have been used to make refrigerators, dish washers, rice cookers, plastic film, chopping boards, vacuum bottles, plastic pails, and garbage containers. Other materials in which antibiotic zeolites have been incorporated include flooring, wall paper, cloth, paint, napkins, plastic automobile parts, catheters, bicycles, pens, toys, sand, and concrete. Examples of such uses are described in U.S. Patents 5,714,445; 5,697,203; 5,562,872; 5,180,585; 5,714,430; and 5,102,401. These applications involve slow release of antibiotic silver from the zeolite particles which is suitable for the antimicrobial fabric.

Antibiotic zeolites are well-known and can be prepared for use in the present invention using known methods. These include the antibiotic zeolites disclosed, for example, in U.S. Patent Nos. 4,938,958 and 4,911,898.

In one embodiment of the invention, the inorganic antibiotic metal containing composition is an antibiotic metal salt. Such salts include silver iodate, silver iodide, silver nitrate, and silver oxide. Silver nitrate is preferred. These salts are particularly quick acting, as no release from ceramic particles is necessary to function antimicrobially.

Antibiotic ceramic particles useful with the present invention include zeolites, hydroxyapatite, zirconium phosphates or other ion-exchange ceramics. Hydroxyapatite particles containing antimicrobial metals are described, e.g., in U.S. Patent No. 5,009,898. Zirconium phosphates containing antimicrobial metals are described, e.g., in U.S. Patent Nos. 5,296,238; 5,441,717; and 5,405,644.

Either natural zeolites or synthetic zeolites can be used to make the antibiotic zeolites used in the present invention. "Zeolite" is an aluminosilicate having a three dimensional skeletal structure that is represented by the formula:

$\text{XM}_2/\text{nO-Al}_2\text{O}_3-\text{YSiO}_2-\text{ZH}_2\text{O}$. M represents an ion-exchangeable ion, generally a monovalent or divalent metal ion, n represents the atomic valency of the (metal) ion, X and Y represent coefficients of metal oxide and silica respectively, and Z represents the number of water of crystallization. Examples of such zeolites include A-type zeolites, X-type zeolites, Y-type zeolites, T-type zeolites, high-silica zeolites, sodalite, mordenite, analcrite, clinoptilolite, chabazite and erionite. The present invention is not restricted to use of these specific zeolites.

The ion-exchange capacities of these zeolites are as follows: A-type zeolite = 7 meq/g; X-type zeolite = 6.4 meq/g; Y-type zeolite = 5 meq/g; T-type zeolite = 3.4 meq/g; sodalite = 11.5 meq/g; mordenite = 2.6 meq/g; analcrite = 5 meq/g; clinoptilolite = 2.6 meq/g; chabazite = 5 meq/g; and erionite = 3.8 meq/g. These ion-exchange capacities are sufficient for the zeolites to undergo ion-exchange with ammonium and antibiotic metal ions.

The specific surface area of preferred zeolite particles is preferably at least 150 m²/g (anhydrous zeolite as standard) and the SiO₂/Al₂O₃ mol ratio in the zeolite composition is preferably less than 14, more preferably less than 11.

The antibiotic metal ions used in the antibiotic zeolites should be retained on the zeolite particles through an ion-exchange reaction. Antibiotic metal ions which are adsorbed or attached without an ion-exchange reaction exhibit a decreased bacteriocidal effect and their antibiotic effect is not long-lasting. Nevertheless, it is advantageous for imparting quick antimicrobial action to maintain a sufficient amount of surface adsorbed

metal ion.

In the ion-exchange process, the antibiotic metal ions tend to be converted into their oxides, hydroxides, basic salts etc. either in the micropores or on the surfaces of the zeolite and also tend to deposit there, particularly when the concentration of metal ions in the vicinity of the zeolite surface is high. Such deposition tends to adversely affect the bactericidal properties of ion-exchanged zeolite.

In an embodiment of the antibiotic zeolites, a relatively low degree of ion exchange is employed to obtain superior bactericidal properties. It is believed to be required that at least a portion of the zeolite particles retain metal ions having bactericidal properties at ion-exchangeable sites of the zeolite in an amount less than the ion-exchange saturation capacity of the zeolite. In one embodiment, the zeolite employed in the present invention retains antimicrobial metal ions in an amount up to 41% of the theoretical ion-exchange capacity of the zeolite. Such ion-exchanged zeolite with a relatively low degree of ion-exchange may be prepared by performing ion-exchange using a metal ion solution having a low concentration as compared with solutions conventionally used for ion exchange.

The antibiotic metal ion is preferably present in the range of from about 0.1 to 20wt.% of the zeolite. In one embodiment, the zeolite contain from 0.1 to 20wt.% of silver ions and from 0.1 to 20wt.% of copper or zinc ions. Although ammonium ion can be contained in the zeolite at a concentration of about 20 wt.% or less of the zeolite, it is desirable to limit the content of ammonium ions to from 0.5 to 15 wt.%, preferably 1.5 to 5 wt.%. Weight% described herein is determined for materials dried at temperatures such as 110°C, 250°C or 550°C as this is the temperature employed for the preferred post-manufacturing drying process.

A preferred antibiotic zeolite is type A zeolite containing either a combination of ion-exchanged silver, zinc, and ammonium or silver and ammonium. One such zeolite is manufactured by Shinegawa, Inc. under the product number AW-10N and consists of 0.6% by weight of silver ion-exchanged in Type A zeolite particles having a diameter of about 2.5μ. Another formulation, AJ-10N, consists of about 2% by weight silver ion-exchanged in Type A zeolite particles having a diameter of about 2.5μ. Another formulation, AW-80, contains 0.6% by weight of silver ion-exchanged in Type A zeolite particles having a diameter of about 1.0μ. Another formulation, AJ-80N, consists of about 2% by weight silver ion-exchanged in Type A zeolite particles having a diameter of about 1.0μ. These zeolites

preferably contain about between 0.5% and 25.0% by weight of ion-exchanged ammonium.

In a preferred embodiment, the inorganic antimicrobial agent can be of the type designated HealthShield, which is sold by the assignee of the subject application. This material is basically a zeolite, this being a metal having one or the whole of the metal substituted by at least one kind of an ion exchangeable metal selected from the group consisting of Ag, Cu and Zn. A typical particle size for the agent is between 0.8 and 10 microns. The agent is dispersed on the coating material 18 in the quantity of between 0.5 and 20% by weight, more preferably between 0.5 and 10% and most preferably between 0.5 and 5% of the matter that remains on the fabric, exclusive of the fabric. The particles adhere to the coating material while it is wet and become embedded in the coating material 18 as it dries.

In accordance with the invention, other inorganic antimicrobial agents, i.e., those containing silver, copper, lead, gold tin, zinc and mercury, can be used.

As shown in Fig. 4, after the antimicrobial agent 20 is applied to the wet coating material 18, the product is cured, that is, dried, with air under pressure, for example at 60 psi. This removes all of the matter, coating material and antimicrobial agent, in the fabric pores 14. As shown, each of the fabric fibers has on one surface thereof the coating material 18 in which are the embedded particles of the antimicrobial agent 20. If both surfaces of the fabric are treated, the entirety of the fabric would have the same appearance.

In any case, the fabric pores 14 would be clear. This maintains fabric pliability.

In another embodiment of making the porous antimicrobial fabric, the inorganic antimicrobial is blended into the textile coating material, such as of the type described above. The mixture is then applied to the base fabric by a spraying process, as previously described, or by dipping. Here also, the fabric is preferably held under tension.

This eliminates the step of dusting the fibers with the particles of the agent.

To complete the process for obtaining the porous fabric, in each type of application of the mixture of coating material and antibiotic agent described above, the wet fabric is held under tension and is subjected to a blowing operation to remove matter from the fabric pores. This results in the fabric substantially retaining its porosity. Thus, the fabric will be relatively more flexible than if the pores were not clear.

As explained above, the coating materials can include, for example, acrylic, polyurethane, silicone, latex, polyglycolic lactic acid or other biodegradable polymer, especially one that is a hydrophilic, non-degrading polymer such as a hydrophilic

polyurethane, for example TECOPHILIC which is made by Thermedics. Use of antimicrobial agents in hydrophilic materials is also described in an application filed on even date herewith, assigned attorney docket number 1985/0E556 and entitled "Antibiotic Hydrophilic Polymer Coating". The inorganic antimicrobial agent mixed with the coating material is one of the type discussed above and the concentration of the agent in the dry coating material is 0.01 to 50%, preferably 0.1 to 20% and most preferably from 0.5 to 10%.

The resulting fabric, made either by applying the inorganic agent to an adherent coating material, or as part of a mixture with the coating material by spraying or dipping, is a piece of fabric that is antimicrobial, pliable and porous.

A preferred embodiment of the fabric of the invention utilized the following:

fiber material:	polyester
silicone mixture:	50% RTV and 50% xylene
thickness of silicone layer:	1-5 microns
agent particle size:	1-2.5 microns
agent dispersal factor:	1%
air pressure:	60 psi

15

The antibiotic properties of the antibiotic zeolite particles of the invention may be assayed while in aqueous formulations using conventional assay techniques, including for example determining the minimum growth inhibitory concentration (MIC) with respect to a variety of bacteria, eumycetes and yeast. In such a test, the bacteria listed below 20 may be employed:

25

Bacillus cereus var mycoides,

Escherichia coli,

Pseudomonas aeruginosa,

Staphylococcus aureus,

Streptococcus faecalis,

Aspergillus niger,

Aureobasidium pullulans,

Chaetomium globosum,

30

Gliocladium virens,

Penicillium funiculosum,

Candida albicans,

Saccharomyces cerevisiae,

The assay for determining MIC can be carried out by smearing a solution containing bacteria for inoculation onto a plate culture medium to which a test sample of the encapsulated antibiotic zeolite particles is added in a particular concentration, followed by incubation and culturing of the plate. The MIC is defined as a minimum concentration thereof required for inhibiting the growth of each bacteria.

Safety and biocompatibility tests were conducted on the antibiotic zeolites employed in the invention. ISO 10993-1 procedures were employed. The following results were obtained:

10

Cytotoxicity: Non-Toxic

Acute Systemic Toxicity: Non-Toxic

Intracutaneous Toxicity: Passed

Skin Irritation Test: Non-Irritant

Chronic Toxicity: No Observable Effect

15

In-vitro Hemolysis: Non-Hemolytic

30-day Muscle Implant Test: Passed

60-day Muscle Implant Test: Passed

90-day Muscle Implant Test: Passed

Ames Mutagenicity Test: Passed

20

Pyrogenicity: Non-Pyrogenic

Thus, the antibiotic zeolites are exceptionally suitable under relevant toxicity and biocompatibility standards for use in the fabric.

25

2. Fabric fully coated with inorganic antimicrobial agent By not using the pressurized drying step described above for blowing the matter from the fabric pores, an antimicrobial fabric is formed that is fully coated. That is, the fabric wetted with the coating material and inorganic agent is permitted to dry at ambient temperature or in a slightly heated environment. With this type of drying, it is not necessary to hold the fabric under tension. The resulting fabric product will be fully coated with the mixture of coating material and embedded antimicrobial agent particles.

In a further embodiment of making the fully coated antimicrobial fabric, the blend of the inorganic antimicrobial and elastomeric coating material is kneaded into the fabric. The kneading takes place without the fabric being held under tension. The blend

coats the fabric fibers and fills the pores. The resulting fabric is fully coated with the antimicrobial agent.

3. Fabric With Integral Antimicrobial Agent In this type of fabric, the fibers are either of a plurality of the mono-filament type, such as of a plurality of polyester filaments, formed in bundles, such as by twisting, or of a naturally multi-filament type, such as cotton. The object is that the fibers themselves have spaces, gaps or voids into which the antimicrobial agent can be placed. For example, a dough or slurry of the antimicrobial agent is kneaded into a fabric of this type and the agent will be embedded in the spaces of the bundle of the plurality of mono-filaments forming a fiber or the fiber of natural material. 10 The fabric can be made porous by holding it under tension and blowing out the agent from the pores, as described above. It can be left non-porous by permitting the agent to dry without attempting to remove the particles from the pores.

To make the graft 70, a piece of the fabric of any of the types described above is cut to size and rolled into a generally tubular shape of the required diameter. The edges of 15 the tube are joined together, such as by stitching with sutures or using an acceptable adhesive. Also, some of the coating materials described above have thermosetting properties which would permit joining of the graft tube edges by heat sealing.

As explained above, where the fabric forming the graft is of the fully coated type, it may be desired to coat it with a tissue compatible material such as collagen. This can 20 be accomplished by coating one side of the fabric, to be the outer surface of the graft, with the collagen either before or after the graft is formed. Both surfaces can be coated with the collagen. The collagen coating can be accomplished by spraying, painting, etc. Alternatively, the fabric can be dipped in a collagen solution either before or after the graft is formed.

25

The present invention will hereunder be explained in more detail with reference to the following non-limiting working examples.

Example 1

30 A 1" x 1" sample of knitted polyester, available from Bard Vascular Systems Division as knitted polyester style no. 6103, was coated with an antibiotic hydrophilic coating as follows.

A coating solution containing 2.90% by weight of hydrophilic polyurethane available as Tecophilic™ from Thermedics; 96.81% tetrahydrofuran; and 0.29% AW-10N zeolite, available from Shinagawa, Inc., was prepared and mixed with a high shear mixer.

5 An eye dropper was used to apply the coating solution to the polyester sample. The polyester sample was then sprayed with air to remove excess powder and cure the coating.

Example 2

10 A Dow Shaker Test was performed on the polyester sample prepared in Example 1 (hereafter referred to as Sample A) to determine its inhibitory effect against *S. aureus*. The Dow Shaker Test is based on Dow Corporate Test Method 0923 for testing aerobic bacteria by Dow Chemical. The Dow Shaker Test is described below.

Sample A was sterilized at 121 °C for 15 minutes.

15 A culture tube containing *S. aureus* was prepared by adding one disk of *S. aureus* to the culture tube. From about 2 to 5 ml of broth was added to the culture tube. Then the culture tube was agitated with a vortex mixer until the disk was completely dissolved in the broth. The bacteria in the culture tube were incubated for at least 3 hours at 35 °C. The culture tube was then refrigerated at about 2-8 °C until needed for testing.

20 A 5 ml sample of bacteria from the culture tube was removed and agitated in a vortex mixer. The absorbance of the sample was measured at 475 nm with a spectrophotometer relative to the absorbance of the aforementioned broth. Broth and/or bacteria from the culture tube were added to the sample until an absorbance of about 0.1 absorbance units was obtained. This corresponded to from about 10^5 to about 10^6 colony forming units per milliliter (CFU/ml).

25 5 ml of suspension was extracted from the sample and added to a flask containing 70 ml of sterile buffer. The resulting solution contained from about 10^4 to about 10^5 CFU/ml. The flask was capped and shaken on a wrist action shaker for 1 minute at maximum speed. This is referred to as time "0 hours" below.

30 The number of colony forming units in 1ml of the solution was determined at time 0 hours by the following procedure. 1 ml of solution was extracted from the flask and added to a vial containing 9 ml of buffer solution to form a 10:1 dilution. The solution was repeatedly diluted with buffer solution until a plate count of about 30 to about 200 CFU/ml was obtained.

1 ml of the solution from the flask and each dilution were transferred to separate petri dishes. About 15-20 ml molten agar was added to each dish. Each dish was rotated 10 times clockwise and 10 times counter-clockwise to evenly distribute the agar and bacteria. Then, each dish was incubated for 18-24 hours at 35 °C. A plate count was 5 performed on the petri dish containing from about 30 to about 200 bacteria colony forming units to determine the number of colony forming units.

Also, at time 0 hours, sample A was added to the flask and shaken with a wrist action shaker for 1 hour. The number of colony forming units in 1 ml of the solution in the flask was determined by the procedure above using 2 petri dishes. If the numbers of 10 colony forming units in the 2 petri dishes were not within 15% of each other, the entire Dow Shaker Test was repeated.

The number of colony forming units in 1 ml of the solution was also determined after shaking the flask with a wrist action shaker for 18 and 24 hours.

A control was tested by the same procedure as sample A. The control was a 15 1" x 1" sample of knitted polyester, available from Bard Vascular Systems Division as knitted polyester style no. 6103.

The number of colony forming units at times 0 hours, 1 hour, 18 hours, and 24 hours for sample A and the control are shown in Table 1. The percentage of bacteria killed by sample A and the control at times 1 hour, 18 hours, and 24 hours are shown in 20 Table 2.

Table 1

Sample	Bacteria Counts of <i>S. aureus</i> (Colony Forming Units)			
	0 hours	1 hour	18 hours	24 hours
Sample A	780,000	2,145,000	85,000	3,700
Control	480,000	12,400,00	4,720,00	4,300,000

Table 2

Sample	% Killed		
	1 hour	18 hours	24 hours
Sample A	0	89.10%	99.53%
Control	0	0	0

As indicated in Table 2, Sample A exhibited 99.53% inhibition of *S. aureus* after 24 hours of contact with the bacteria.

WE CLAIM:

- 1 1. A medical graft comprising:
2 a piece of fabric material containing an inorganic antimicrobial agent, said
3 piece of fabric formed in generally tubular shape with said antibiotic agent at least on the
4 interior of said graft.
- 1 2. A graft as in claim 1 further comprising a coating of a tissue compatible
2 material on at least the exterior surface of said graft.
- 1 3. A graft as in claim 1 wherein said fabric is porous.
- 1 4. A graft as in claim 1 wherein said antimicrobial agent is in a coating
2 material coat onto said fabric.
- 1 5. A graft as in claim 4 further comprising a coating of a tissue compatible
2 material on at least the exterior surface of said graft.
- 1 6. A graft as in claim 4 wherein said coating material is elastomeric.
- 1 7. A graft as in claim 4 wherein said coating material is selected from the
2 group consisting of acrylic, polyurethane, silicone, latex, polyglycolic lactic acid, a
3 biodegradable polymer, a hydrophilic biodegradable polymer, and a non-degrading polymer.
- 1 8. A graft as in claim 7 wherein said non-degrading polymer is a hydrophilic
2 polyurethane.
- 1 9. A graft as in claim 7 wherein the fibers of said fabric are selected from the
2 group consisting of cotton, nylon, polyester, Teflon, e-PTFE and blends of these materials.
- 1 10. A graft as in claim 1 wherein said antimicrobial agent is a metal.
- 1 11. A graft as in claim 1 wherein said antimicrobial agent is a zeolite.

1 12. A graft as in claim 1 wherein said agent is dispersed on the coating
2 material in the quantity of between 0.5 and 20% by weight, more preferably between 0.5 and
3 10% and most preferably between 0.5 and 5% of the matter that remains on the fabric,
4 exclusive of the fabric

1 13. A graft as in claim 12 wherein the particle size of said agent is between
2 0.8 and 10 microns.

1 14. A method of making a medical graft comprising:
2 providing a fabric containing an inorganic antimicrobial agent; and
3 forming said fabric piece in a generally tubular shape to form said graft with
4 said antibiotic agent at least on the interior of said graft.

1 15. A method as in claim 14 further comprising the step of coating at least
2 the outer surface of said graft with a tissue compatible material.

1 16. A method as in claim 14 wherein said piece of fabric is porous.

1 17. A method as in claim 16 wherein the step of providing said piece of
2 porous fabric comprises:
3 applying a coating material containing said antimicrobial agent to cover the
4 fabric piece and removing matter from the fabric pores.

1 18. A method as in claim 17 wherein said applying step comprises first
2 applying a wet coating material to said fabric and then applying said antimicrobial agent in
3 powdered form to the wet coating material.

1 19. A method as in claim 17 wherein said applying step comprises applying
2 a mixture of said coating material and said antimicrobial agent to said fabric.

1 20. A method as in claim 17 wherein said removing step comprises applying
2 a gas under pressure to said fabric.

1 21. A method as in claim 17 wherein said fabric is held under tension during
2 the application of said coating material.

1 22. A method as in claim 17 wherein said fabric piece is held under tension
2 during application of said coating material and removing of said matter in said fabric pores.

1 23. A method of producing a pliable antimicrobial fabric comprising:
2 providing a piece of porous fabric; and
3 applying material containing an inorganic antimicrobial agent to said fabric
4 while leaving pores of said fabric open.

1 24. A method as in claim 23 wherein said applying step comprises:
2 applying a coating material and said antimicrobial agent to cover the fabric
3 piece and removing matter from the fabric pores.

1 25. A method as in claim 24 wherein said applying step comprises first
2 applying a wet coating material to said fabric and then applying said antimicrobial agent in
3 powdered form said wet coating material.

1 26. A method as in claim 24 wherein said applying step comprises applying
2 a mixture of said coating material and said antimicrobial agent to said fabric.

1 27. A method as in claim 24 wherein said removing step comprises applying
2 a gas under pressure to said fabric.

1 28. A method as in claim 24 wherein said fabric is held under tension during
2 the application of said coating material.

1 29. A method as in claim 24 wherein said fabric piece is held under tension
2 during application of said coating material and during removing of said matter from said
3 fabric pores.

1 30. A method as in claim 23 wherein the fibers of said fabric piece are of a
2 type having voids and the step of applying comprises placing said antimicrobial agent into
3 said voids.

1 31. A pliable antimicrobial fabric comprising:
2 a piece of porous fabric containing an inorganic antimicrobial agent on the
3 fabric fibers with the pores of said fabric piece left open.

1 32. A pliable antimicrobial fabric as in claim 31 wherein said antimicrobial
2 agent is in a coating on the fibers of said fabric piece.

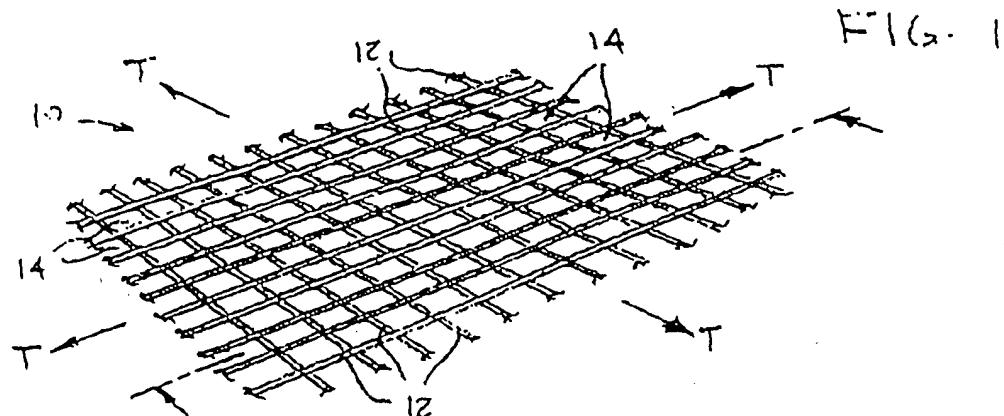
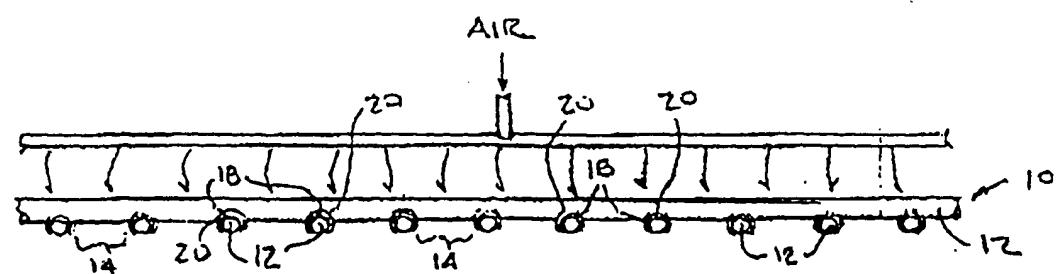
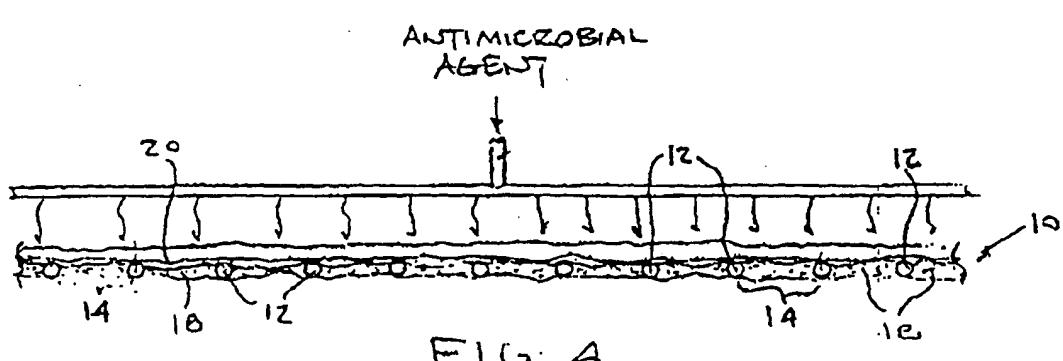
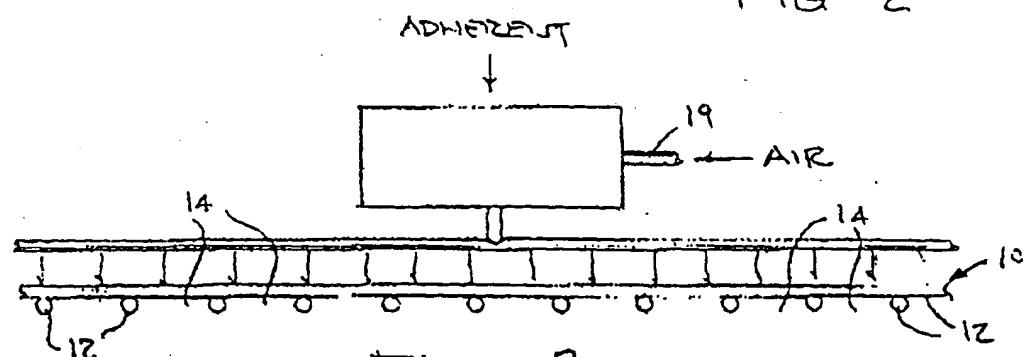
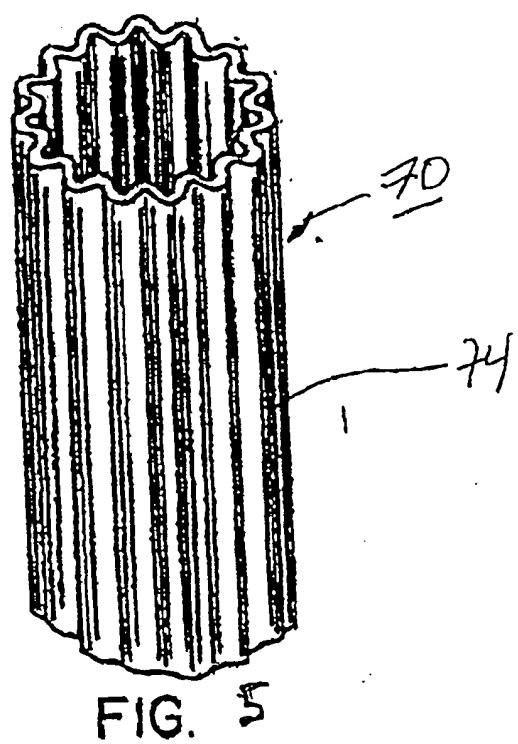


FIG. 2





**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.